REMARKS

Claims 1 and 3-19 are pending with claims 5-16 being withdrawn, claim 2 being cancelled and claim 1 being amended herein.

Statement of Substance of the Interview

Applicants would like to thank Examiner Celsa for his time and comments in the interview of February 19, 2004.

During the interview, Applicants focused primarily on the Lee et al. reference (discussed further below) and the appropriate interpretation of the Lee et al. reference. As noted in the interview, Dr. Saksela was the head of the laboratory that conducted the work described in Lee et al. As such, Dr. Saksela is an expert authority on the teachings of the reference.

During the interview, the Examiner suggested that the claims be amended to further remove any inadvertent overlap with Lee et al. The claims have thusly been amended, as discussed below. In addition, Dr. Saksela provided letters from several peers in the field who stated that, in their opinion, the invention could not be predicted from the work disclosed in Lee et al. any they considered the invention to be an unexpected improvement over anything previously known in the field. As requested by the Examiner, the authors of the letters have incorporated their opinion into formal declarations, which are submitted herewith under 37 C.F.C.§1.132.

Rejections under 35 U.S.C. §102(b)/103

Claims 1-4 have been rejected under 35 U.S.C. §102(b)/103 as being anticipated by or obvious over Lee et al. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

As noted during the interview, Dr. Saksela was the head of the laboratory that conducted the work reported in Lee et al. and thus is undoubtedly an authority of the work disclosed in Lee et al. and the conclusions that may be reached from the reference. In Lee et al., Dr. Saksela's lab had no intention of creating a truly artificial SH3 domain, i.e. an SH3 domain that is completely unknown in nature.

In Lee et al. the amino acid sequence as not changed by "random" mutations. The online Mirriam-Webster Online dictionary defines "at random" as "without definite aim, direction, rule, or method." Similarly, "yourdictionary.com" defines "random" as "Having no specific pattern, purpose, or objective." The work reported in Lee et al. in no way could be considered "random" mutations. There was a definite aim, i.e. to make one naturally occurring SH3 domain look like another, with a definite pattern and method, i.e. use directed mutagenesis replace specific amino acids in the sequence of one SH3 domain with the known amino acids of another naturally occurring SH3 domain. Thus, Lee et

al. does not use or suggest "randomized" mutation of the SH3 domain.

Specifically, in Lee et al. the SH3 domain of Fyn was mutated to have corresponding amino acids of Hck. The researchers found that by replacing amino acids in the Fyn SH3 domain with Hck amino acids, the binding of Fyn to Nef resembled that of Hck. However, while the binding affinity of the Fyn mutant was higher than the wild-type Fyn, the binding was never greater than binding occurring in nature, i.e. the binding affinity of wild-type Hck. Thus, while the mutant Fyn binding affinity was higher than that of wild-type Fyn, the binding of the mutant Fyn was never greater than wild-type Hck. While Lee et al. may teach modifying the Fyn SH3 domain, the modifications were only to replicate the naturally occurring SH3 domains of other naturally occurring proteins. There was no intent, suggestion or contemplation by the authors of Lee et al. to create a truly artificial sequence, i.e. a sequence not occurring any where in nature. As such, the work of Lee et al. neither anticipates nor suggests the presently claimed method.

During the interview, the Examiner offered very helpful comments for further clarifying the invention from the work in Lee et al. As noted on the Interview Summary Record, the Examiner suggested amending the claims to specifically recite that the region being mutated is within the variable region of an

RT loop the would correspond to amino acids 69-74 of Hck. Claim 1 has been amended as indicated above to define the mutated region as being the variable region of an RT loop that corresponds to amino acids 69-74 of Hck. This region is well known and has been well characterized with proteins having an SH3 domains. Attached hereto as Exhibit A is an amino acid sequence alignment showing the variable region of RT loops that corresponds to amino acids 69-74 of Hck for over one hundred different proteins. Thus, one skilled in the art would readily know what region of a particular protein is the variable region of an RT loop that corresponds to amino acids 69-74 of Hck, and therefore should be randomly mutated in the claimed method.

2) During the interview the Examiner observed that the binding of the mutated SH3 domains is in the context of the protein, rather than a peptide fragment. The Examiner requested that the claims be amended to recite that the "protein" has a higher affinity than the wild-type. Claim 1 has been thusly amended.

3) During the interview, Dr. Saksela provided letters from several peers in the field, who professed the opinion that the claimed invention is not suggested by the work of Lee et al. In addition, the ability to reach higher than naturally occurring binding using the claimed method was a complete surprise to the

scientists who wrote the letters. The Examiner requested that the opinions stated in the letters be presented in formal declarations under 37 C.F.R.§132.

Attached hereto are declarations from each of Dr. Mauno VIHINEN; Dr. Marius SUDOL and Dr. Bruce MAYER. Drs. VIHINEN, SUDOL and MAYER are all experts in the field of SH3 domains and are knowledgeable as to the state of the art at the time of the invention and what one skilled in the art would have been able to predict based on the work of Lee et al. All three experts conclude that 1) the work of Lee et al. is different from that of the present invention; 2) there is no suggestion in Lee et al. of the present invention; and 3) the finding that with the invention that SH3 domains can be generated that have higher than any naturally occurring affinities it completely unexpected.

Also attached hereto is a declaration submitted under 37 C.F.R.§1.132 of Dr. Chi-Hon LEE, the first named author of the Lee et al. article. Dr. Lee himself states that the work presented in the Lee et al. article was different from and did not suggest the invention and even more importantly Dr. Lee found the results obtained with the present method "astonishing" and "a surprise."

The four attached declarations clearly evidence that the present invention is distinct and original from the method used in Lee et al. and the present invention achieves unexpected results which in no way could be predicted from the Lee et al.

article. As such, the present invention is neither anticipated by nor obvious over Lee et al. and withdrawal of the rejection is respectfully requested.

Claims 1-4 and 17-19 have also been rejected under 35 U.S.C. §103 as being obvious over Lee et al. combined with Sparks et al. As noted during the interview, the invention is not suggested even if the teachings of Sparks et al. are combined with Lee et al.

As stated above, Lee et al. fails to teach that by producing a collection of DNA fragments encoding SH3 domains containing a randomized mutations in a variable domain of an RT-loop (RRT-SH3 domains) that corresponds to amino acids 69-74 of Hck, non-naturally occurring RT-loop domains can be obtained, which have greater than naturally occurring binding affinity. Sparks et al. fails to make up for the deficiencies in Lee et al., in part, because Sparks et al. teach that it is the conserved, i.e. not the variable, region that is important for SH3 domain binding. This is in opposite with the present invention which found that the key to creating unexpected improved binding resides in the variable domain being randomly mutated. Thus, there is no suggestion of the present invention in the combined teachings of Lee et al. and Sparks et al.

Should the Examiner have any questions regarding the present application he is requested to please contact MaryAnne Armstrong,

PhD (Reg. No. 40,069) in the Washington DC area at (703) 205-8000.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Exhibit A; Declarations of Drs. Drs. VIHINEN, SUDOL, MAYER and LEE